

A new focus on tyrosine kinases inhibitors in eosinophilic granulomatosis with polyangiitis

Sirs,

The recent editorial by Rossi *et al.* describes new therapeutics for anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) (1). As stated by the authors, despite the knowledge of the AAV has been revolutionised, several issues remain, especially concerning the management of eosinophilic granulomatosis with polyangiitis (EGPA). New insights into pathogenetic mechanisms and evidence-based data can lead to disease-/patient-tailored therapeutics (1).

Here we report the rare case of familial ANCA-positive EGPA (2) with concomitant FIP1L1-PDGFRa (F/P)-unmutated chronic eosinophilic leukaemia (CEL) who was successfully treated with imatinib mesylate (IM), a small-molecule tyrosine kinase inhibitor (TKi).

A 50-year-old Caucasian male referred to our Clinic almost one year ago presenting past medical history significant for hypereosinophilic nasal polyposis and severe bronchial asthma with PR-3 antigen positivity. Psoriasis (PsO) was documented in his father while PR-3-EGPA occurred in his brother who came to death in young age for acute intestinal ischaemia. At the time, a diagnosis of PR-3-EGPA was made and the patient was treated with steroids (3). Nevertheless, severe dysphagia required gastroscopy with histology that showed eosinophilic gastritis (EG). An extensive blood work up documented the F/P-unmutated CEL and, in 2015, IM was introduced (200 mg/day) in combination with hydroxyurea (500 mg/day) with rapid efficacy on gastrointestinal symptoms and eosinophil count (4). However, in 2018, the patient showed inflammatory painful shoulders and bilateral swelling of ankles and feet. High levels of acute-phase reactants (CRP 28 mg/dl) were registered while no abnormalities in serum uric acid, rheumatoid factor, and anti-cyclic-citrullinated-peptide antibodies were observed; HLA-B27 resulted negative. Ultrasonography (US) registered significant structural enthesal changes at 6 sites: supraspinatus and subscapularis insertions into the superior facet of the humerus (bilateral) with subacromial bursitis (right); posterior tibial tendon (right); flexor hallucis tendon (right). Fluid distention and synovial thickening resulted at US study of tibiotarsal and metatarsophalangeal joints (bilateral) with peroneal tenosynovitis (right). Magnetic resonance imaging (MRI) of right ankle and feet confirmed US findings (Fig. 1). A diagnosis of PsA *sine* clinically overt PsO was established with a baseline high disease activity (Disease Activity Index for PsA, DAPSA = 28). The small molecule

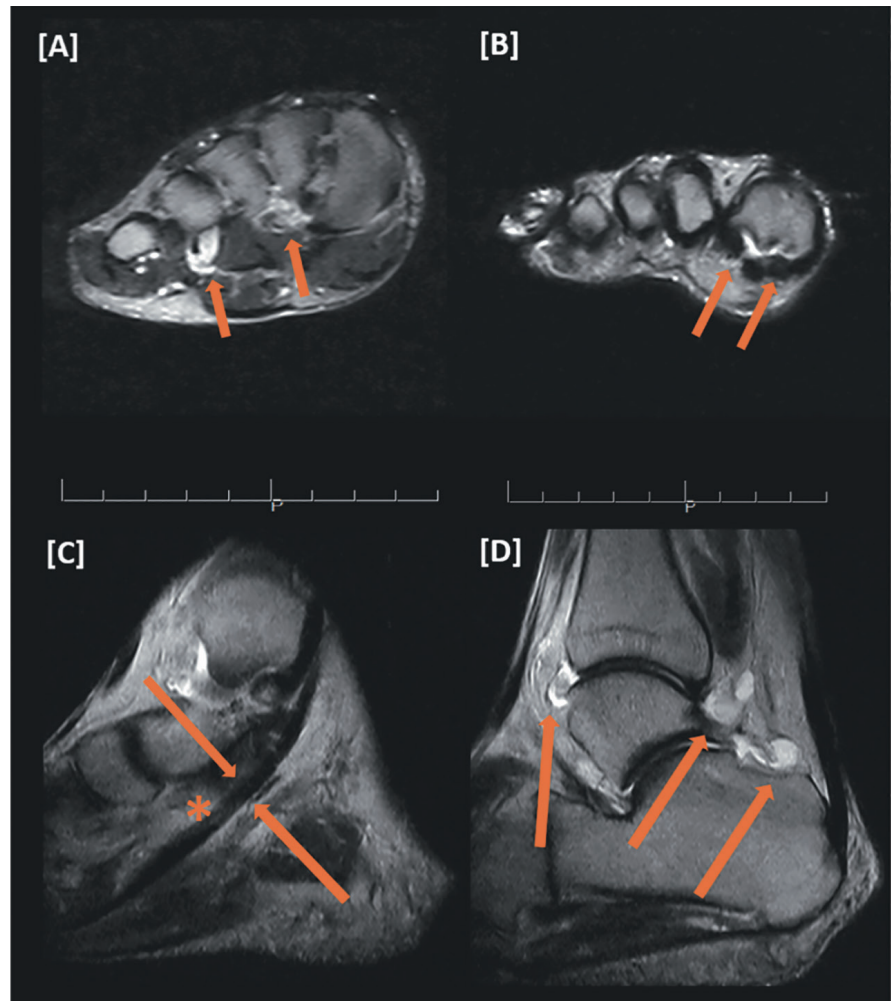


Fig. 1. Magnetic resonance imaging (MRI) representative findings from right ankle and foot. Fat saturation T2-weighted fast spin-echo MRI. Axial plane of right foot showed up soft tissue subcutaneous swelling of forefoot (A) and effusion of 1 metatarsophalangeal joint (B). Sagittal plane of the right ankle depicted hyperintensity (*) and thickened of distal posterior tibial tendon (C) and synovial joint effusion at tibiotarsal joint extending into anteroinferior Kager's fat pad (D).

phosphodiesterase-4 inhibitor (apremilast) was added to therapy (30 mg twice daily) leading to an early and persistent disease remission (DAPSA=2). At the time of reporting (10 months of therapy), the patient is still in haematological remission, with a good asthma control and endoscopic/histologic follow up reporting no EG flares. In accordance with our report, IM resulted as a highly effective treatment for the control of both EGPA and CEL, even though CEL was F/P-unmutated. As suggested by evidence, a possible pathogenic role for IM-sensitive TK supports IM as a promising therapy in EGPA, and controlled trials should be required to validate therapeutic potential of IM targeting at cases with contraindications or resistance to conventional therapy (5-7). As known, most of the IM-toxicity occurs within the first 2 years of therapy, appears mild-to-moderate and potentially reversible. Although studies are available so far on effective TKi treatment in inflammatory arthritis (8, 9), herein, we report for the first time a possible IM-

driven arthritis, challenging a potential *ca-veat* on long-term IM toxicity. Even though the PsA onset in this patient after 3-year IM could well be coincidental, particularly as the patient had a family history of PsO, there is some evidence showing that TKi possess a weak off-target activity driving paradoxical Raf/MEK/ERK-NF- κ B activation that, under some circumstances, may contribute to the development of inflammatory diseases (10).

In conclusion, TKi can be useful, as steroid sparing and "non-conventional" immunosuppressant agents, in the induction and maintenance of remission in EGPA, in accordance with the idea of a tailored therapy.

Acknowledgements

The author thanks Dr Federico Sabuzi for assistance in MRI image interpretation and for his helpful suggestions on an earlier draft of this letter (Dipartimento di Diagnostica per Immagini, Imaging Molecolare, Radiologia Interventistica e Radioterapia, Rome, Italy).

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Competing interests: none declared.

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